REMARKS

Reconsideration is requested.

Claims 43-58 are pending.

The specification has been amended to incorporate subject matter from the recited WO 92/13943, by reference to a recently issued related U.S. Patent No. 6,040,169, which is based thereon. The applicants respectfully submit the subject matter is now properly incorporated by reference, pursuant to MPEP §608.01(p). The Examiner is requested to contact the undersigned if anything further is required in this regard. Withdrawal of the objection stated at ¶4, of page 2, of the Office Action dated March 1, 2000, (Paper No. 21) is requested.

Prior to responding to the specific claim rejections, the applicants present the following restatement of the present invention and its contribution to the art.

The invention relates to a method of treating a metastaitic tumour which occurs in, but does not originate from, the central nervous system of a human. The method requires the step of administering an effective amount of a mutant HSV-1 which has a non-functional γ34.5 gene in the long repeat region (R_1).

The invention is based on the discovery that HSV which is γ34.5 null is effective against non-neuronal cancers. This is surprising as HSV was known in the art to selectively inhabit the neuronal system. Thus, it was unexpected that such an HSV mutant could be effective against cancers of a non-neuronal origin.

At the time the application was filed, various HSV-1 mutants were known (R3616,1714 and 1716) and work had been carried out showing their selectiveness to inhabit the neuronal system. Therefore, until the present invention, the use of these mutants on cancers of a non-neuronal origin was neither known or assumed.

The substantial contribution to the art made by the present inventors is the disclosure for the first time that such mutants may be used to treat metastatic tumours which occur in, but do not originate from, the central nervous system. This contribution has been made in the form, for example, of an application for a patent so that a reasonable protection of the invention can be obtained in return. Therefore, in return for a patent, the inventors give as consideration a complete revelation or disclosure of the invention for which protection is sought.

The Section 112, first paragraph, rejection of claims 43-50 and 52-57, stated at ¶5 of Paper No. 21, is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner's rejection appears to be based on two premises. Firstly, the Examiner appears to believe that the specification and common general knowledge in the art does not enable the production of the HSV-1 mutants; and secondly, that the specification does not provide enablement for the treatment of a metastatic tumour or melanoma comprising administering HSV-1 mutant, or the treatment of a melanoma in a human comprising administering HSV-1 mutant. (The Examiner is requested to advise the undersigned if the applicants' understanding of the rejection is incorrect and provide a further opportunity to respond, prior to the Examiner's issuance of a further Action.) The applicants respectively disagree with both of these premises, for the reasons provided below. However, firstly, a review of the general principles for determining enablement are provided.

It is stated in patent law that the specification must include a written description of the invention or discovery and of the manner and process of making the same, and is required to be in such full and clear, concise, and exact terms as to enable any person skilled in the art or

science to which the invention or discovery appertains, or with which it is most nearly connected to make and use the same.

The applicants respectfully submit that the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v Hyde , 242 US 261, 270 (1916) which posed the question is the experimentation needed to practice the invention undue or reasonable?

The fact that experimentation may be complex does not make it undue, if the art typically engages in such experimentation. In In re Wands, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), the court noted that the nature of monoclonal antibody technology is such that experiments first involve the entire attempt to make monoclonal hybridomas to determine which one secrete antibody with the desired characteristics. Id. at 1406-1407 The court found that :

1) The specification provided direction and guidance and presented working examples;

2) All the methods needed to practice the invention were well known; and

3) There was a high level of skill in the art at the time the application was filed.

The situation with regard to enablement has been summarised in other court decisions. For example, the applicants respectfully submit that all which is necessary is that one skilled in the art be able to practice the invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement issue of 35 USC 112 is satisfied. Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 USC 112.

The production of HSV-1 mutants

The Examiner states that she has not found the arguments submitted by the applicants in the last response persuasive because (a) the cited case DeGeorge v Bernier relates to a different technical field and thus, "the findings in said case cannot be extrapolated to the enablement of the instant invention."; and (b) "the mutants as claimed are unlimited and can be made in any portion of the HSV-1" and so "[o]ne skilled in the art is limited to essentially random production of mutants". See, pages 3-4 of Paper No. 21.

The principles of patentability are the same irrespective of the technical field. The applicants do not rely on the "findings" of the previously cited case but rather the application of the law stated therein. The statement selected from DeGeorge v Bernier referred to "an invention" in general and not to the specific invention of the case. Thus, it is submitted that the statement "An inventor need not, however, explain every detail since he is speaking to those skilled in the art" is as applicable to inventions in the biotech field as it is the field of a data processing system printer.

With regard to statement "the mutants as claimed are unlimited and can be made in any portion of the HSV-1" , the applicants note that this interpretation of the invention is incorrect. In accordance with well established patent law, the scope and meaning of the claims must be interpreted in light of the specification. During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. Further, the broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach

Pending claim 43 states "a mutant herpes simplex virus type 1 which has a non-functional γ34.5 gene in the long repeat region (R_L)." The specification teaches that the terminal 1 kb of the

long repeat region (R_L) of the HSV-1 and HSV-2 genomes contain a gene (Ackermann et al 1986, Chou et al 1990, and McGeoch et al 1991). Deletion or mutation of this gene (γ34.5), results in variants that grow as well as wild type virus on dividing cells of many established cell lines, but show impaired replication on non-dividing cells (Chou et al 1990, McGeoch et al 1991 and Bolovan et al 1994). The specification also provides information on a mutant known in the art (R3616) that contains a 1000bp deletion in γ34.5 and provides details as to the production of another known mutant virus (1716) that has a 759bp deletion in γ34.5 (Maclean et al 1991).

The summary of the invention in the specification states the use of a mutant HSV which has been modified in the γ34.5 gene of the long repeat region (R_L) such that the gene is non-functional.

Further, the specification defines the term "non-functional" as meaning that the gene has been modified by deletion, insertion or substitution (or other change in the DNA sequence such as rearrangement) such that it does not express the normal product or a functionally equivalent product.

Thus, the description "a non-functional γ34.5 gene in the long repeat region (R_L)" would be understood by the skilled person as meaning that the γ34.5 gene has been modified such that it does not express the normal product or a functionally equivalent product. This interpretation is entirely consistent with the description of the invention contained in the specification and with the working examples provided.

Therefore, contrary to the Examiner's assertions, the mutants claimed are not unlimited. In fact, the claim defines a small specific class of HSV-1 mutants in that they not only must

contain a modified γ34.5 gene in the long repeat (R_L), but also, that modification must result in the gene not being able to express the normal product or a functionally equivalent product.

In summary, claim 43 relates to a method of using a specific class of HSV-1 mutants. The specific class of mutants is not claimed, contrary to the Examiner's statement on page 4, line 5 of Paper No. 21, as they are acknowledged to be already known in the art. Indeed, not only are various mutants known in the art, but the production of such mutants is well established given the details available on the structure of HSV-1, its genetic layout and molecular biological techniques known in the art.

The Examiner has acknowledged that the inventors have provided a working example for the production of a specific mutant (1716) having a deletion with γ34.5. This specific mutant has a deletion of 759bp within this gene. For argument sake, the applicants submit that a third party arriving at a mutant having an 800bp deletion within the γ34.5 gene, such that the mutant had the same properties as 1716, may gain the advantages of the present invention by using this alternative mutant to treat metastatic cancers of non-neuronal origin without any inventive input of their own. This scenario does not serve the rewards offered by the patent system in providing protection with a limited monopoly in return for complete disclosure. The applicants have provided a new method for the treatment of cancers using a specific known class of HSV-1 mutants previously believed not to have the properties required to allow this method to be successful. It is submitted to be inappropriate to require that the scope of protection allowed for such a discovery is the use of one specific mutant of this class rather than other members known or obtainable by routine methods.

The established case law on enablement agrees that claims are enabled if any of the following conditions are met.

1) The specification must provide direction and guidance and present working examples;

2) All the methods needed to practice the invention are well known; and

3) There was a high level of skill in the art at the time the application was filed.
It is submitted that the present application meets all of the conditions provided above.

1) The specification provides information about the art and directs the skilled person to disclosures relating to the production of HSV-1 mutants falling within the class claimed (see page 3 and page 4 of the present specification). The specification further provides working examples on the production of such mutants and details as to how this teaching could be generalised so as to produce those alternative mutants. For example, it is suggested on page 5 and page 6 that modification of the γ34.5 gene may be effected at a point within the gene generally corresponding to a restriction enzyme site. The description further provides details of a fragment between two Bam H1 restriction sites and suggests this as a location for the modification. The skilled person is then taught that the modification may be a deletion of about 0.1 kb to 3kb in length. Therefore, plenty of guidance is provided within the specification as to how to produce alternative mutants not specifically disclosed in the working examples or already known in the art.

2) All of the methods required to produce the mutants are detailed in the specification or specifically cross-referenced. However, even though the relevant information has been provided, all of the methods required to work the invention are well known in the art. For example, standard molecular biological techniques are described in Sambrook, Fritsch and Maniatis, "Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1989.

3) A high level of skill existed at the time the present invention. This can be shown by the large number of groups that were working in the field of HSV-1 and the fact that other mutated strains existed in the art e.g. R3616.

Withdrawal of the Section 112, first paragraph, rejection of claims 43-50 and 52-57, is requested.

The Section 112, first paragraph, rejection of claims 43-50 and 52-57, as stated in ¶6 of Paper No. 21, is traversed. Reconsideration and withdrawal of the rejection is are requested in view of the following comments.

The Examiner has rejected claims 43-50 and 52-57 because, in the Examiner's opinion, the specification does not enable "a method of treating a metastatic tumour or melanoma comprising administering mutant HSV, wherein the HSV-1 has a non-functional gamma 34.5 gene in the long repeat region." See, page 4 of Paper No. 21.

The applicants note that no objection has been raised against claim 51. Therefore, the applicants assume that the Examiner believes that a method of treating a metastatic tumour or melanoma comprising administering mutant 1716 is enabled.

The Examiner has acknowledge that the specification does enable an aspect of the claimed invention, namely, "a method of treating a metastatic tumour which occurs in but does not originate from the CNS comprising intra tumoral or intracranial injection of HSV-1 wherein the HSV-1 has a non-functional gamma 34.5 gene in the long repeat region, wherein HSV-1 infects the tumor cells of the tumor."

Thus, it would appear that the specification is enabled for all of the claimed mutants to treat a metastatic tumour where the mutant is injected into the tumour itself, whereas only mutant 1716 is enabled for the broader scope of the claims, namely administration in general. The Examiner is requested to provide further clarification of her position in the event this is a misstatement of the rejection.

Clarification is requested as it is not understood why if all mutants are enabled for one type of administration, why only one mutant is enable for a broader scope of administration. For example, the Examiner has accepted that with regard to the intratumoral or intracranial injection, the specification is enabling for all possible mutants falling within the scope of the claim. In other words, the Examiner has accepted that the various mutants will have the same therapeutic effect owing to the modification of the γ34.5 gene. However, given this, it is not understood why the specific mutant 1716 is enabled for a broader scope of administration whereas other mutants are not. In order to have accepted that all forms of mutant are enabled for a particular form of treatment, the Examiner must have concluded that the mutants have the same therapeutic effect owing to their modification. Therefore, it does not follow that mutant 1716 is enabled for a broader scope of administration whereas other forms of mutant, having the same therapeutic properties, are not.

The Examiner has further objected to, in her opinion, the lack of teaching in the specification concerning the targeting of the mutants to the tumours in question. However, the specification itself provides extensive examples as to the use of the mutant viruses in the treatment of brain tumours. Not only does the specification provide guidance as to the use of HSV-1 mutant strains *in vivo* but also provides evidence of use on human cells, obviously *in vitro*.

Specifically, Example 3 shows the treatment of brain tumours with HSV-1 mutant 1716 *in vivo*. Example 6 shows the effects on human cells *in vitro*. Example 7 illustrates that HSV-1 strain 1716 cannot be detected in the mouse CNS following intracerebral inoculation. Example 8 shows that strain 1716 lytically replicates in NT2 tumours (Ntera-2 cells) but not in transplanted NT2N cells (differentiated) in the mouse CNS. This example further illustrates the ability of

strain 1716 to induce regression of brain tumours (NT2 tumours in the brain). Fig, 6 E-G shows that a significant regression of the tumour occurred.

Example 10 illustrates the long-term survival of HSV strain 1716 treated tumour bearing mice. It was shown that those mice treated with strain 1716 there was only evidence of fibrotic scar tissue and dystrophic calcifications but no evidence of residual live tumour cells. Further, the brains of the mice were negative for herpes antigens indicating the absence of replicating virus.

Thus, the specification itself provides detailed example of the use of mutant strains of HSV-1 on metastatic tumours which occur in but do not originate from the CNS. The skilled person would be left in no difficulty in order to determine a route of administration as this has been clearly illustrated in the example, albeit on mice.

Withdrawal of the rejection of claims 43-50 and 52-57, is requested.

The Section 112, first paragraph, rejection of claims 51 and 58 is obviated by the attached Deposit Receipt and the following comment that any and all restrictions imposed by the Depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent. Withdrawal of the Section 112, first paragraph, rejection of claims 51 and 58, is requested.

The Section 103 rejection of claims 43-58 over U.S. Patent No. 5,585,096 in view of Olofsson (Arch. Virol., 1993, 123, 128: 241-256), Davey (Neurosurgery, 1991, 28: 8-14), WO 92/13943 and Market (Neurosurgery, 1993, 32: 597-603) is traversed. Reconsideration and withdrawal of the rejections are requested in view of the following distinguishing comments.

U.S. Patent No. 5,585,096 relates to a replication competent HSV that is capable of killing nervous system tumour cells. The virus in question is described as a replication competent

HSV that is incapable of expressing (i) a functional γ34.5 gene product and (ii) a ribonucleotide reductase.

The patent is concerned with the treatment of malignant brain tumour cells and tumours cells of a nervous system type. Thus, this patent teaches away from the invention defined in claims 43 to 51.

However, the patent makes a passing reference to the possible treatment of "other kinds of tumour cells" and lists melanoma cells within this class. Although there is this brief reference to melanoma cells, all examples and explanation provided in the patent specification relate to the treatment of primary brain tumours. There is no actual teaching relating to the use of a HSV-1 mutant virus (different to that of the present invention in that it is required to be incapable of expressing a ribonucleotide reductase) in the treatment of any tumour other than a primary brain tumour.

Thus, this patent document does not teach the mutant virus of the present invention nor does it teach the class of tumours that can be treated by the mutant virus of the present invention other than a brief reference to melanoma.

The applicants respectfully submit that in order for a claimed invention to be obvious over a prior art reference, or a collection of references, at least three basic criteria must be met:

1) there must be some suggestion or motivation, either in the cited references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

2) there must be a reasonable expectation of success - not to be confused with an obvious desire to succeed; and

3) the prior art reference or references must teach or suggest all of the claim limitations.

Further, if an independent claim is non-obvious under 35 U.S.C. 103, then any claim depending therefrom is non-obvious.

Therefore, in relation to the present case the following comments are directed to independent claims 43 and 52 only.

Taking the above points in turn. The teaching or suggestion to make the claimed combination (the HSV-1 mutant virus in accordance with the invention) and the reasonable expectation of success (the successful treatment of metastatic tumours which occur in but do not originate from the CNS, and the treatment of melanoma) must both be found in the prior art and not based on applicants disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1488 (Fed. Cir. 1991).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. Further, with regard to an expectation of success, at least some degree of predictability is required. In other words, the expectation of some advantage is the strongest rationale for combining references.

In the present case, it is submitted that, even if the mere reference to melanoma cells in U.S. Patent No. 5,585,096 is taken to be a motivation to treat this sort of tumour with the mutant virus described in U.S. Patent No. 5,585,096, this still does not show that such use would be attempted with any reasonable expectation of success. Indeed, U.S. Patent No. 5,585,096 is specifically concerned with the treatment of primary tumours in the CNS. As HSV is known to inhabit the brain and the nervous system, the use of this virus in the treatment of primary

tumours originating within the brain and nervous system may be considered with an expectation of success. However, the treatment of secondary (metastatic) tumours which do not originate from the nervous system would not have been considered with any expectation of success. Indeed, of the four references cited by the Examiner, this distinction in tumour types is not acknowledged nor is it suggested that HSV-1 could be used in the treatment of such non-originating brain tumours.

The Examiner has cited Davey et al., which discuss the treatment of cerebral metastases from malignant melanoma. This document is concerned only with radiotherapy and does not mention the use of any viral treatment. Therefore, it is submitted that the first criteria required for showing obviousness has not been met in that the ordinarily skilled person would not have combined the teaching of this document with that of U.S. Patent No. 5,585,096 as they concern different technical fields.

As mentioned above, the present invention is based on the discovery that the specific HSV-1 mutant of the present invention can be successfully used with advantageous results in the treatment of tumours of non-CNS origin. This was not known at the filing date of the application and there was no teaching or suggestion available in the cited prior art that would have motivated the ordinarily skilled person to use such a mutant (disclosed only in WO 92/13943) on such tumours with any reasonable expectation of success given the available knowledge on HSV, namely, that it inhabits cells of the brain and nervous systems.

Accordingly, withdrawal of the Section 103 rejection of claims 43-58 is requested.

In view of the above and attached, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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